A Facile Synthesis of Substituted 3-Amino-1*H*-Quinazoline-2,4-Diones

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A new synthesis of a series of 3-amino-1*H*-quinazoline-2,4-diones is described. The 1*H*-quinazoline-2,4-dione **10** was made starting with fluorobenzoic acid in three high yielding steps. The key step of this synthesis involved the generation of the dianion of urea **7** and the subsequent intramolecular nucleophilic displacement of the 2-fluoro to form the quinazolinedione ring. The 3-amino moiety was incorporated using (2,4-dinitro-phenyl)-hydroxylamine as the aminating reagent.

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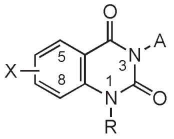
Recently we reported on the 3-hydroxy-1*H*-quinazoline-2,4-diones as a novel class of antibacterial agents [1]. In a continuing effort to expand our understanding of structure-activity relationships (SAR) within this class, we found that replacing the 3-hydroxyl with an amino group afforded compounds with even more potent activity. Herein, we disclose our synthetic efforts toward construction of this altered chemotype.

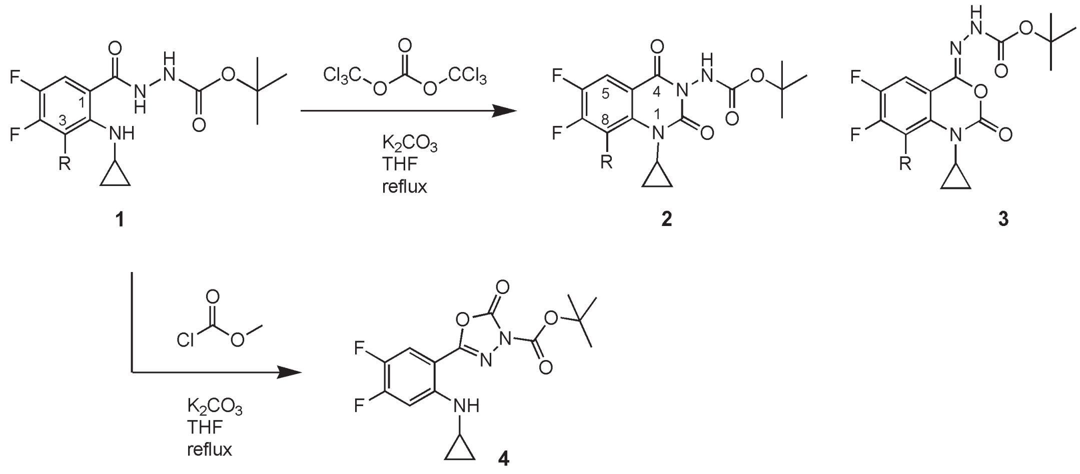


A = OH; 3-hydroxy-1*H*-quinazoline-2,4-diones
A = NH_2; 3-amino-1*H*-quinazoline-2,4-diones

Synthesis of the 3-amino-1*H*-quinazoline-2,4-dione ring system has been reported in the literature. The first reported synthesis involved a reaction of hydrazine hydrate with a 3*H*-quinazolinedione under harsh conditions [2]. Other reported approaches include reaction of *t*-butyl carbazate with isatoic anhydride [3], treatment of 2-aminobenzoylhydrazine with urea [4], ring contraction of the 7-membered 1,3,4-benzotriazepine-2,5-dione ring with sodium hydroxide [5], and reaction of 4-oxo-4*H*-3,1-benzoxazine-2-carbonitrile with hydrazine hydrate [6].

Initially, we envisioned synthesizing the 3-aminoquinazolinedione nucleus by a ring closure of a substituted-(2-amino-4-fluorobenzoyl)hydrazinecarboxylic acid *tert*-butyl ester with triphosgene [7,8,9], followed by displacement of the 7-fluoro of the synthesized Boc-protected 3-aminoquinazolinedione core with various nucleophilic side chains, typically 3-substituted pyrrolidines [1]. Removal of the Boc-protecting group under acidic conditions would then generate the desired targets. Reducing

Scheme 1



this concept to practice with the *N'*-(2-cyclopropylamino-benzoyl)-hydrazinecarboxylic acid *tert*-butyl ester precursor **1** (R= H) unexpectedly did not give the desired quinazolinedione **2**, but instead afforded the corresponding (2-oxo-1,2-dihydro-benzo[*d*][1,3]oxazin-4-ylidene)-hydrazinecarboxylic acid *tert*-butyl ester **3** (Scheme 1). Compound **3** was stable to chromatographic isolation and its structure was confirmed by X-ray crystallography (Figure 1). The cyclopropyl substituent was chosen because of its importance to the Structure Activity Relationship (SAR) of this series.

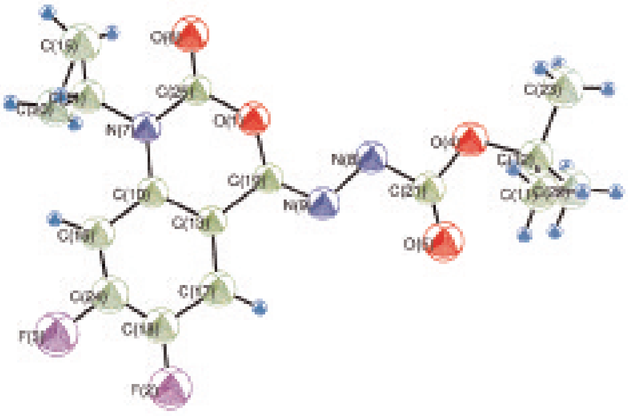


Figure 1. X-ray crystal structure of (2-oxo-1,2-dihydro-benzo[*d*][1,3]-oxazin-4-ylidene)-hydrazinecarboxylic acid *tert*-butyl ester (**3**).

Further examination of the above reaction revealed that the product formed was dependent on the 3-substitution (R) of **1**. Unlike the above 3-unsubstituted example, we found that the 3-chloro, 3-methyl, and 3-methoxy substrates afforded exclusively the desired quinazolinedione product **2**. Interestingly, reaction of the 3-fluoro analogue gave a mixture of both products **2** and **3**. These results are summarized in Table 1. Thus, it appears that the pathway of the ring-closure with triphosgene was determined only by the steric hindrance imposed by the 3-substituent, and not the electronic effect of this group. Aside from X-ray crystallography, the only difference between products of type **2** and **3** was evident in their ^{1}H NMR spectra. In deuterated chloroform, the –NH proton of **2** was observed as a broad singlet in the region of 6.7-6.8 ppm, whereas that of **3** was shifted significantly downfield, typically found at around 8.2 ppm.

Table 1

Ring Formation: Ratio of Products as Determined by the 3-Substituent of **1**

R	Quinazolinedione **2**	Benzooxazin-4-ylidine **3**
H	-	100
F	80	20
Cl	100	-
Me	100	-
Ome	100	-

Attempts to form the quinazolinedione ring with methyl chloroformate, as previously reported [10,11], also did not give the desired quinazolinedione **2**. Surprisingly, the reaction yielded yet a different product, oxadiazole **4** (Scheme 1), whose structure was verified by X-ray crystallography (Figure 2).

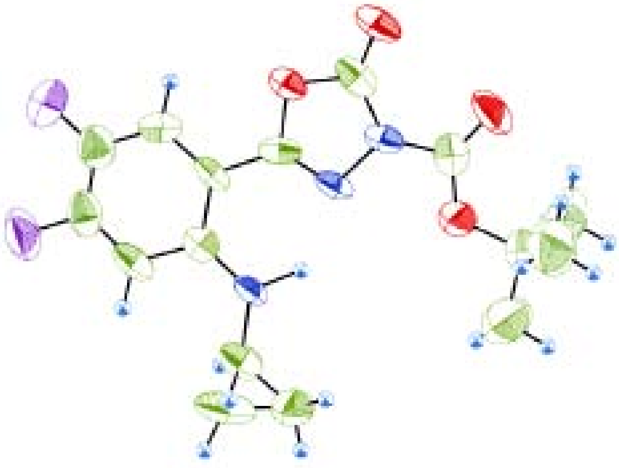
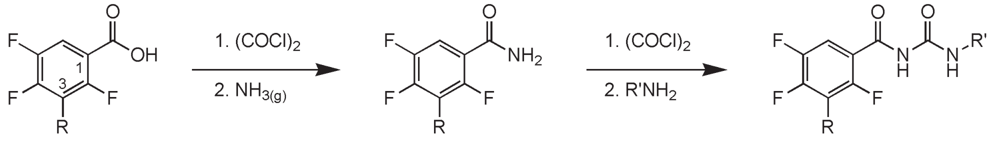


Figure 2. X-ray crystal structure of oxadiazole **4**.

Because the 1- and 8-substituents on the 3-aminoquinazolinedione ring system play a prominent role in determining biological activity, we sought a synthesis that would allow us to efficiently explore the SAR at these positions. Consequently, we decided to explore the approach shown in Scheme 2. Starting with commercially available 2-fluorobenzoic acid **5**, we reacted it with oxalyl chloride in the presence of catalytic amount of *N*,*N*-dimethylformamide to provide the acid chloride, which was treated immediately with gaseous ammonia to cleanly give amide **6** in high yield. Other groups have reported different synthetic approaches to amides **6a-c** [12]. Amide **6** was again treated with oxalyl chloride at elevated temperature to generate the corresponding benzoyl isocyanate [13]. Upon complete formation, the highly reactive isocyanate was quickly reacted with a primary amine to give urea **7**. The amines shown (cyclopropylamine, isopropylamine, and aniline) were chosen based on SAR considerations as well as to demonstrate the broad application of our synthetic method. While all three amines confer varying degrees of steric hindrance, cyclopropylamine and aniline additionally possess reduced basicity and nucleoplilicity.

Scheme 2



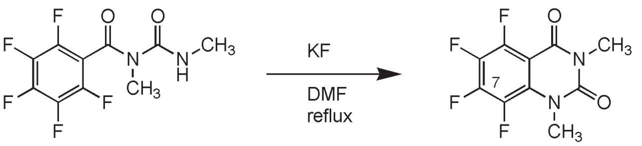
5a, R= H
5b, R= Me
5c, R= OMe

6a, R= H : 75%
6b, R= Me : 100%
6c, R= OMe : 100%

7a, R= H; R'= cyclopropyl : 87%
7b, R= Me; R'= cyclopropyl : 93%
7c, R= Me; R'= Ph : 96%
7d, R= OMe; R'= cyclopropyl : 90%
7e, R= OMe; R'= isopropyl : 75%

The next step involved the intramolecular cyclization of urea **7** to form the quinazolinedione ring system. Precedence for this conversion had been established in the synthesis of tetrafluoro-1,3-dimethyl-1*H*-quinazoline-2,4-dione **9** [14], formed in moderate yield by treatment of 1,3-dimethyl-1-pentafluorobenzoylurea **8** with potassium fluoride in *N,N*-dimethylformamide at reflux (Scheme 3). Similar reaction with sodium hydride led instead to further displacement of the 7-fluoro substituent of **9** with dimethylamine, presumably formed from slow breakdown of the solvent *N,N*-dimethylformamide.

Scheme 3



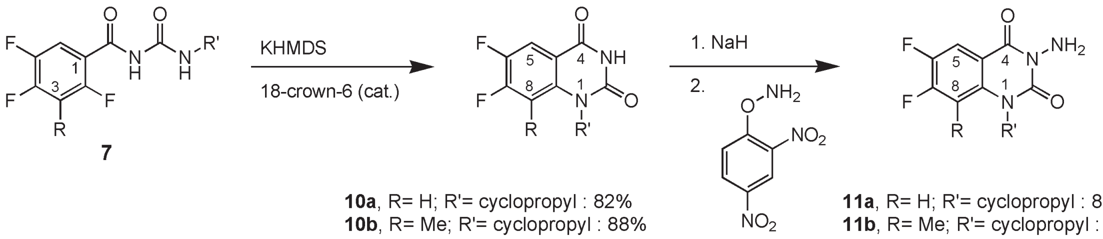
8 **9**

In our series, the dianion of urea **7** must be generated in order to facilitate the ring closure. The proximal –NH is more acidic but the anion of the distal –NH is the nucleophile needed to intramolecularly displace the 2-fluoro substituent. As such, more than two equivalents of a strong base was required to completely generate the dianion of **7**. We found that sodium and potassium bis(trimethylsilyl)amide were suitable bases for this transformation. In particular, using potassium bis(trimethylsilyl)amide along with a catalytic amount of 18-crown-6 in tetrahydrofuran consistently gave high yields of **10** (Scheme 4).

Utilizing classical literature procedures to synthesize 1*H*-quinazoline-2,4-diones (*e.g.*, Ref. 2-6, Scheme 1 above) requires installation of the 1-substituent by alkylation of a precursor anthranilic acid building block. This places a severe limit on the substituents that can be installed onto this position. However, for our route, the synthesis of **10a**, **10b**, **10c**, and **10d** demonstrates its wide-ranging utility. The *N*-1 cyclopropyl and phenyl groups, which cannot be easily installed *via N*-alkylation, were readily incorporated during the formation of urea **7** and then cyclized to their respective quinazolinedione **10**. There was no observed difference between the alkyl (**10b**) and aromatic (**10c**) substituent in the ring-closure reaction as both were formed in comparably high yields (88% and 93%, respectively) under identical reaction conditions. Furthermore, neither steric or electronic requirements imposed by R and R' hinder the cyclization of urea **7** to quinazolinedione **10** as evidenced by the favorable yields of all the examples shown.

The final step of our synthesis involved the installation of an amino group at the 3-position. Penultimate **10** was reacted with sodium hydride, and the resulting anion was treated with the aminating reagent, *o*-(2,4-dinitrophenyl)-

Scheme 4



7

10a, R= H; R'= cyclopropyl : 82%
10b, R= Me; R'= cyclopropyl : 88%
10c, R= Me; R'= Ph : 93%
10d, R= OMe; R'= cyclopropyl : 84%
10e, R= OMe; R'= isopropyl : 73%

11a, R= H; R'= cyclopropyl : 85%
11b, R= Me; R'= cyclopropyl : 80%
11c, R= Me; R'= Ph : 70%
11d, R= OMe; R'= cyclopropyl : 89%
11e, R= OMe; R'= isopropyl : 73%

hydroxylamine [15], to afford the target 3-amino-1*H*-quinazoline-2,4-dione **11** in straightforward fashion. The synthesis of compounds **11b** and **11d** has been disclosed using alternative aminating reagents [16].

In conclusion, we have developed a highly efficient synthesis for the 3-amino-1*H*-quinazoline-2,4-dione ring. From any starting 2-fluorobenzoic acid, a corresponding 3-aminoquinazolinedione can be synthesized in four steps. The approach described allows much flexibility for substitutions, especially at the 1- and 8-positions of the 3-aminoquinazolinedione core.

EXPERIMENTAL

All ^{1}H and ^{19}F NMR were recorded at 400 MHz using a Varian Inova spectrometer equipped with an ATB probe and two RF channels. Positive and negative ion atmospheric pressure chemical ionization (APCI) mass spectra were obtained on a Micromass Platform LC mass spectrometer operating in Open Access mode. Samples were introduced by loop injection using a Gilson 215 autosampler into a mobile phase of 80:20 acetonitrile:water flowing at 200 µL/min delivered by a Hewlett-Packard HP1100 HPLC. The mass spectrometer source and probe temperatures were 150 °C and 450 °C, respectively. The cone voltage was 15 V while the corona pin was held at 3.5 kV in positive ion and 3.0 kV in negative ion mode. Elemental analyses were performed by Quantitative Technologies, Inc. Unless stated otherwise, concentration of solvents utilized in reactions and workups was conducted under reduced pressure. Anhydrous magnesium sulfate was used to dry the organic phase during workup.

General Procedure for the Preparation of Substituted Trifluorobenzamide **6**.

To a stirred solution of commercially available trifluorobenzoic acid **5a-c** in dichloromethane at room temperature was added oxalyl chloride (1.2 eq) followed by *N,N*-dimethylformamide (0.1 eq). After 90 min, the reaction mixture was concentrated. The resulting acid chloride was taken up in dichloromethane, cooled to 0 °C, then ammonia gas was added *via* a dispersion tube until the solution was saturated. The solution was stirred for 2 h, and then concentrated to a residue that was triturated in diethyl ether to afford amide **6a-c** as a solid.

2,4,5-Trifluoro-benzamide (**6a**).

This compound was obtained in 75% yield; ^{1}H NMR (CDCl$_3$): δ 5.88 (br s, 1H), 6.58 (br s, 1H), 6.95-7.02 (m, 1H), 7.91-7.98 (m, 1H); ^{19}F NMR: δ -114 (m, 1F), -126 (m, 1F), -140 (m, 1F); MS (APCI+): *m/z* 176 (M+H)$^+$.

Anal. Calcd. for $C_7H_4F_3N_1O_1$: C, 48.01; H, 2.30; N, 8.00, F, 32.55. Found: C, 48.05; H, 2.09; N, 7.71; F, 32.60.

2,4,5-Trifluoro-3-methyl-benzamide (**6b**).

This compound was obtained in 100% yield; ^{1}H NMR (CDCl$_3$): δ 2.28 (apparent t, *J* = 2.2 Hz, 3H), 5.99 (br s, 1H), 6.65 (br s, 1H), 7.77-7.84 (m, 1H); ^{19}F NMR: δ -118 (m, 1F), -130 (m, 1F), -141 (m, 1F); MS (APCI+): *m/z* 190 (M+H)$^+$.

Anal. Calcd. for $C_8H_6F_3N_1O_1$: C, 50.80; H, 3.20; N, 7.41, F, 30.13. Found: C, 50.76; H, 2.94; N, 7.31; F, 30.14.

2,4,5-Trifluoro-3-methoxy-benzamide (**6c**).

This compound was obtained in 100% yield; ^{1}H NMR (CDCl$_3$): δ 4.06 (apparent t, *J* = 0.9 Hz, 3H), 5.92 (br s, 1H), 6.54 (br s, 1H), 7.58-7.65 (m, 1H); ^{19}F NMR: δ -133 (m, 1F), -138 (m, 1F), -144 (m, 1F); MS (APCI+): *m/z* 206 (M+H)$^+$.

General Procedure for the Preparation of the 1-Substituted-3-(2,4,5-trifluoro-benzoyl)-urea **7**.

To a solution of trifluoro-benzamide **6a-c** in 1,2-dichloroethane at room temperature was added oxalyl chloride (1.5 eq). The reaction mixture was heated at reflux for 4 h, and then concentrated. The resulting benzoyl isocyanate was dissolved in *p*-dioxane, the resultant solution cooled to 0 °C and then treated with a primary amine (1.2 eq). The reaction mixture was allowed to gradually warm to room temperature over a 4 h period. The mixture was concentrated to a residue, was dissolved in dichloromethane, and the solution was washed successively with saturated aqueous sodium bicarbonate, water, and brine, and then dried. Concentration of the organic phase provided a residue that was triturated in diethyl ether - hexanes to afford urea **7a-e** as a solid. The filtrate was processed as above to afford a second crop.

1-Cyclopropyl-3-(2,4,5-trifluoro-benzoyl)-urea (**7a**).

This compound was obtained in 87% yield; ^{1}H NMR (CDCl$_3$): δ 0.55-0.65 (m, 2H), 0.76-0.82 (m, 2H), 2.71-2.78 (m, 1H), 7.00-7.07 (m, 1H), 7.82-7.89 (m, 1H), 8.40 (br s, 1H), 8.44 (br s, 1H); ^{19}F NMR: δ -112 (m, 1F), -123 (m, 1F), -139 (m, 1F); MS (APCI+): *m/z* 259 (M+H)$^+$.

1-Cyclopropyl-3-(2,4,5-trifluoro-3-methyl-benzoyl)-urea (**7b**).

This compound was obtained in 93% yield; ^{1}H NMR (CDCl$_3$): δ 0.61-0.65 (m, 2H), 0.80-0.85 (m, 2H), 2.29 (apparent t, *J* = 2.2, 3H), 2.75-2.81 (m, 1H), 7.66-7.73 (m, 1H), 8.49 (br s, 1H), 8.53 (br s, 1H); ^{19}F NMR: δ -116 (m, 1F), -127 (m, 1F), -140 (m, 1F); MS (APCI+): *m/z* 273 (M+H)$^+$.

1-Phenyl-3-(2,4,5-trifluoro-3-methyl-benzoyl)-urea (**7c**).

This compound was obtained in 96% yield; ^{1}H NMR (d$_6$-DMSO): δ 2.19 (s, 3H), 7.08 (t, *J* = 7.4 Hz, 1H), 7.30 (t, *J* = 7.6 Hz, 1H), 7.50 (d, *J* = 7.6 Hz, 1H), 7.65 (apparent q, *J* = 6.6 Hz, 1H), 10.28 (br s, 1H), 11.04 (br s, 1H); ^{19}F NMR: δ -118 (m, 1F), -132 (m, 1F), -142 (m, 1F); MS (APCI+): *m/z* 309 (M+H)$^+$.

Anal. Calcd. for $C_{15}H_{11}F_3N_2O_2$: C, 58.45; H, 3.60; N, 9.09, F, 18.49. Found: C, 58.30; H, 3.31; N, 8.97; F, 18.40.

1-Cyclopropyl-3-(2,4,5-trifluoro-3-methoxy-benzoyl)-urea (**7d**).

This compound was obtained in 90% yield; ^{1}H NMR (CDCl$_3$): δ 0.57-0.62 (m, 2H), 0.76-0.81 (m, 2H), 2.71-2.77 (m, 1H), 4.03 (s, 3H), 7.46-7.53 (m, 1H), 8.35 (br s, 1H), 8.38 (br s, 1H); ^{19}F NMR: δ -132 (m, 1F), -137 (m, 1F), -141 (m, 1F); MS (APCI+): *m/z* 289 (M+H)$^+$.

Anal. Calcd. for $C_{12}H_{11}F_3N_2O_3$: C, 50.01; H, 3.85; N, 9.72, F, 19.77. Found: C, 49.94; H, 3.65; N, 9.91; F, 19.45.

1-Isopropyl-3-(2,4,5-trifluoro-3-methoxy-benzoyl)-urea (**7e**).

This compound was obtained in 75% yield; ^{1}H NMR (CDCl$_3$): δ 1.21 (d, *J* = 6.6 Hz, 6H), 3.98-4.03 (m, 1H), 4.03 (apparent t, *J* = 1.1 Hz, 3H), 7.47-7.54 (m, 1H), 8.20 (br d, *J* = 5.4 Hz, 1H), 8.39 (br d, *J* = 11.8, 1H); ^{19}F NMR δ -132 (m, 1F), -137 (m, 1F), -142 (m, 1F); MS (APCI+): *m/z* 291 (M+H)$^+$.

Anal. Calcd. for $C_{12}H_{13}F_3N_2O_3$: C, 49.66; H, 4.51; N, 9.65, F, 19.64. Found: C, 49.82; H, 4.22; N, 9.68; F, 19.41.

General Procedure for the Preparation of Substituted 1*H*-Quinazoline-2,4-Dione (**10**).

To a -10 °C solution of urea **7a-e** in tetrahydrofuran was added dropwise potassium bis(trimethylsilyl)amide (0.5 *M* in toluene, 2.1 eq). Following addition, the reaction mixture was warmed to room temperature, treated with 18-crown-6 (0.2 eq), and then heated at reflux for 90 min. The mixture was cooled to room temperature, diluted with ethyl acetate, and the solution was washed successively with 1 *N* aqueous hydrochloric acid, water, and brine. The organic phase was dried and concentrated to a residue that was triturated in diethyl ether - hexanes to afford quinazolinedione **10a-e** as a solid. Further processing of the filtrate as above afforded a second crop.

1-Cyclopropyl-6,7-difluoro-1*H*-quinazoline-2,4-dione (**10a**).

This compound was obtained in 82% yield; ^{1}H NMR (d_6-DMSO): δ 0.77-0.81 (m, 2H), 1.17-1.22 (m, 2H), 2.76-2.82 (m, 1H), 7.68-7.73 (m, 1H), 7.87-7.91 (m, 1H), 11.55 (br s, 1H); ^{19}F NMR: δ -127 (m, 1F), -145 (m, 1F); MS (APCI-): *m/z* 237 (M-H)$^-$.

1-Cyclopropyl-6,7-difluoro-8-methyl-1*H*-quinazoline-2,4-dione (**10b**).

This compound was obtained in 88% yield; ^{1}H NMR (d_6-DMSO): δ 0.54-0.59 (m, 2H), 0.96-1.02 (m, 2H), 2.48 (d, *J* = 3.3 Hz, 3H), 3.27-3.31 (m, 1H), 7.64 (t, J= 9.4 Hz), 11.49 (br s, 1H); ^{19}F NMR: δ -129 (m, 1F), -143 (m, 1F); MS (APCI-): *m/z* 251 (M-H)$^-$.

Anal. Calcd. for $C_{12}H_{10}F_2N_2O_2$: C, 57.15; H, 4.00; N, 11.11, F, 15.06. Found: C, 57.16; H, 3.96; N, 11.12; F, 14.80.

1-Phenyl-6,7-difluoro-8-methyl1*H*-quinazoline-2,4-dione (**10c**).

This compound was obtained in 93% yield; ^{1}H NMR ($CDCl_3$): δ 1.49 (d, *J* = 3.3 Hz, 3H), 7.27-7.29 (m, 2H), 7.40-7.48 (m, 3H), 7.89 (t, *J* = 8.9 Hz, 1H), 8.26 (br s, 1H); ^{19}F NMR: δ -124 (m, 1F), -140 (m, 1F); MS (APCI-): *m/z* 287 (M-H)$^-$.

1-Cyclopropyl-6,7-difluoro-8-methoxy-1*H*-quinazoline-2,4-dione (**10d**).

This compound was obtained in 84% yield; ^{1}H NMR (d_6-DMSO): δ 0.56-0.61 (m, 2H), 0.91-0.96 (m, 2H), 3.12-3.18 (m, 1H), 3.88 (d, *J* = 1.5 Hz), 7.55-7.60 (m, 1H), 11.51 (br s, 1H); ^{19}F NMR: δ -141 (m, 1F), -144 (m, 1F); MS (APCI-): *m/z* 267 (M-H)$^-$.

Anal. Calcd. for $C_{12}H_{10}F_2N_2O_3$: C, 53.74; H, 3.76; N, 10.44, F, 14.17. Found: C, 53.67; H, 3.51; N, 10.32; F, 13.81.

1-Isopropyl-6,7-difluoro-8-methoxy-1*H*-quinazoline-2,4-dione (**10e**).

This compound was obtained in 73% yield; ^{1}H NMR (d_6-DMSO): δ 1.44 (d, *J* = 6.8 Hz, 6H), 3.92 (d, *J* = 1.6 Hz, 3H), 4.65 (septet, *J* = 6.6 Hz, 1H), 7.60-7.65 (m, 1H), 11.55 (br s, 1H); ^{19}F NMR: δ -141 (m, 1F), -143 (m, 1F); MS (APCI-): *m/z* 269 (M-H)$^-$.

Anal. Calcd. for $C_{12}H_{12}F_2N_2O_3$: C, 53.34; H, 4.48; N, 10.37, F, 17.76. Found: C, 53.62; H, 4.29; N, 10.15; F, 14.04.

General Procedure for the Preparation of Substituted 3-Amino-1*H*-Quinazoline-2,4-Dione (**11**).

To a 0 °C solution of quinazolinedione **10a-e** in tetrahydrofuran was added portion-wise sodium hydride (60% in mineral oil, 1.2 eq). The reaction mixture was warmed to room temperature for 30 min, and then treated with (2,4-dinitro-phenyl)-hydroxylamine (1.2 eq). The reaction mixture was heated at reflux for 90 min, cooled to room temperature, and then diluted with ethyl acetate. The solution was washed successively with saturated aqueous ammonium chloride, water, and brine. The organic phase was dried and concentrated to a residue that was triturated in dichloromethane - diethyl ether to afford 3-amino-quinazolinedione **11a-e** as a solid. The filtrate was concentrated to a residue that was purified *via* flash column chromatography (ethyl acetate/hexanes gradient) to afford a second crop.

3-Amino-1-cyclopropyl-6,7-difluoro-1*H*-quinazoline-2,4-dione (**11a**).

This compound was obtained in 85% yield; ^{1}H NMR (d_6-DMSO): δ 0.74-0.82 (m, 2H), 1.16-1.25 (m, 2H), 2.85-2.73 (m, 1H), 5.50 (br s, 2H), 7.69-7.75 (m, 1H), 7.88-7.94 (m, 1H); ^{19}F NMR: δ -128 (m, 1F), -144 (m, 1F); MS (APCI+): *m/z* 254 (M+H)$^+$.

3-Amino-1-cyclopropyl-6,7-difluoro-8-methyl-1*H*-quinazoline-2,4-dione (**11b**).

This compound was obtained in 80% yield; ^{1}H NMR (d_6-DMSO): δ 0.56-0.60 (m, 2H), 0.99-1.03 (m, 2H), 2.50 (d, *J* = 3.3 Hz, 3H), 3.38-3.43 (m, 1H), 5.40 (br s, 2H), 7.71 (t, *J* = 9.4 Hz, 1H); ^{19}F NMR: δ -129 (m, 1F), -143 (m, 1F); MS (APCI+): *m/z* 268 (M+H)$^+$.

3-Amino-1-phenyl-6,7-difluoro-1*H*-quinazoline-2,4-dione (**11c**).

This compound was obtained in 70% yield; ^{1}H NMR ($CDCl_3$): δ 1.49 (d, *J* = 2.9 Hz, 3H), 5.26 (br s, 2H), 7.27-7.30 (m, 2H), 7.43-7.49 (m, 3H), 7.95 (t, *J* = 8.8 Hz, 1H); ^{19}F NMR: δ -125 (m, 1F), -140 (m, 1F); MS (APCI+): *m/z* 304 (M+H)$^+$.

Anal. Calcd. for $C_{15}H_{11}F_2N_3O_3$: C, 59.41; H, 3.66; N, 13.86, F, 12.53. Found: C, 59.18; H, 3.43; N, 13.66; F, 12.64.

3-Amino-1-cyclopropyl-6,7-difluoro-8-methoxy-1*H*-quinazoline-2,4-dione (**11d**).

This compound was obtained in 89% yield; ^{1}H NMR (d_6-DMSO): δ 0.58-0.62 (m, 2H), 0.94-0.99 (m, 2H), 3.26-3.31 (m, 1H), 3.89 (d, *J* = 1.8 Hz, 3H), 5.42 (br s, 2H), 7.61-7.66 (m, 1H); ^{19}F NMR: δ -141 (m, 1F), -145 (m, 1F); MS (APCI+): *m/z* 284 (M+H)$^+$.

Anal. Calcd. for $C_{12}H_{11}F_2N_3O_3$: C, 50.89; H, 3.91; N, 14.84. Found: C, 50.69; H, 3.62; N, 14.61%.

3-Amino-1-isopropyl-6,7-difluoro-8-methoxy-1*H*-quinazoline-2,4-dione (**11e**).

This compound was obtained in 73% yield; ^{1}H NMR (d_6-DMSO): δ 1.47 (d, *J* = 6.6 Hz, 6H), 3.94 (d, *J* = 1.7 Hz, 3H), 4.75 (septet, *J* = 6.6 Hz, 1H), 5.50 (br s, 2H), 7.66-7.71 (m, 1H); ^{19}F NMR: δ -141 (m, 1F), -143 (m, 1F); MS (APCI+): *m/z* 286 (M+H)$^+$.

Anal. Calcd. for $C_{12}H_{13}F_2N_3O_3$: C, 50.53; H, 4.59; N, 14.73. Found: C, 50.16; H, 4.59; N, 14.55.

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